

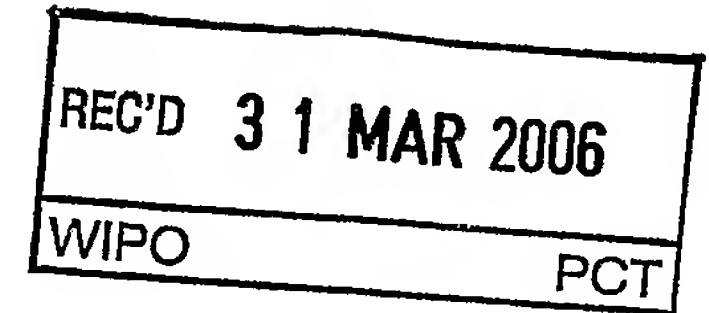
PATENT COOPERATION TREATY


PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference C163517PC ADI/jhl	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/EP2004/013907	International filing date (day/month/year) 07.12.2004	Priority date (day/month/year) 29.12.2003	
International Patent Classification (IPC) or national classification and IPC INV. A61K38/20 A61K7/06 A01K67/027 A61P17/14			
Applicant UNIVERSITÄTSKLINIKUM MÜNSTER et al.			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 9 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau) a total of 6 sheets, as follows:</p> <p style="margin-left: 40px;"><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p style="margin-left: 40px;"><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input checked="" type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand 07.01.2005		Date of completion of this report 28.03.2006	
Name and mailing address of the international preliminary examining authority:  European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840		Authorized officer Ceder, O Telephone No. +49 30 25901-342	



INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/013907

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1, 2, 5-29	as originally filed
3, 4	received on 02.09.2005 with letter of 01.09.2005

Sequence listings part of the description, Pages

1-5	as originally filed
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Claims, Numbers

1-23	received on 02.09.2005 with letter of 01.09.2005
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Drawings, Sheets

1/5-4/5	as originally filed
5/5	received on 02.09.2005 with letter of 01.09.2005

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/013907

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 15 and 23 with respect to industrial applicability

because:

- ☒ the said international application, or the said claims Nos. 15 and 23 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/013907

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	3, 4, 8-22
	No: Claims	1, 2, 5-7, 23
Inventive step (IS)	Yes: Claims	
	No: Claims	1-23
Industrial applicability (IA)	Yes: Claims	1-14, 16-22
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2004/013907

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☒ contained in the international application as filed
 - ☒ filed together with the international application in computer readable form
 - ☐ furnished subsequently to this Authority for the purposes of search and/or examination
 - ☐ received by this Authority as an amendment on
2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional observations, if necessary:

Re Item III

Non-establishment of opinion with regard to industrial applicability

Claims 15 and 23 relate, at least partly, to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Documents

1.1 Reference is made to the following documents:

- 1.2 **D1:** Lindner et al., J. Invest. Dermatol., vol. 110, 1998, pp. 457-458
D2: US2003/0114526

2. Novelty (Art. 33(2) PCT)

- 2.1 The present application does not satisfy the criterion set forth in Article 33(2) PCT because **the subject-matter of claims 1, 2, 5-7 and 23 is not new** in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).
- 2.2 The present application is concerned with the use of IL-15 polynucleotides, polypeptides and/or agonists for the stimulation of hair growth.
- 2.3 Document **D1** discloses (page 457, right-hand column, fourth paragraph; page 458, left-hand column) the inhibitory effect of IL-15 on keratinocyte apoptosis in hair bulbs. The

inhibition of apoptosis of the hair bulbs must at least implicitly be considered as stimulation of hair growth. **D1** further suggests the use of IL-15 receptor agonists in chemotherapy-induced alopecia.

2.4 Document **D1**, thus, explicitly or implicitly, destroys the novelty of claims 1, 2, 5-7 and 23.

2.5 Claims 3, 4, and 8-22 contains subject-matter that is novel over the cited prior art.

3. Inventive step (Art. 33(3) PCT)

3.1 The present application does not satisfy the criterion set forth in Article 33(3) PCT, because **the subject-matter of claims 1-23 does not involve an inventive step** (Rule 65(1)(2) PCT).

3.2 Even if claim 1 could be considered novel, it can not be considered inventive over **D1**. Document **D1** discloses the use of IL-15 to inhibit apoptosis in hair bulbs in vivo (page 457, right-hand column, fourth paragraph; page 458, left-hand column) and suggests its relevance in alopecia. A decreased apoptosis (death of cells) must be considered positive for the possibility of the hair bulbs to continue to produce hair. A dead cell does not produce any hair. The person skilled in the art, trying to find a method to increase the production/growth of hair would, thus, have the incentive to try and use IL-15 to decrease the death of cells and increase the potential of hair growth. In doing so he would arrive at the subject-matter of claim 1. No inventive activity can thus be acknowledged for claim 1 or 2.

3.3 Claim 3 is concerned with the use of IL-15 polynucleotides, polypeptides and/or agonists for the stimulation of hair growth, together with a second hair growth stimulating compound.

3.4 The subject-matter of claim 3, differs from that of **D1**, in that it concerns the use of a second active compound together with IL-15.

- 3.5 This difference can, however, not be considered as involving an inventive step (Article 33(3) PCT). The use of additional active compounds in compositions for affecting hair growth is already known, e.g. from **D2** (claim 8). It would be obvious for a person skilled in the art to combine the teachings of **D1** with the additional compounds of **D2** to arrive to the subject-matter of present claims 3 and 4. No inventive activity can, therefore, be acknowledged for claims 3 and 4.
- 3.6 None of claims 5-13 seem to contain any subject-matter which together with the subject-matter with any of the claims they depend upon could form the basis for an inventive activity.
- 3.7 Claim 14 is concerned with a transgenic animal expressing the state of the art IL-15 polynucleotide of claim 1. To obtain a transgenic animal expressing a known nucleic acid can not be considered inventive, but is only the mere application of state of the art technology, known to any person skilled in the art. Claim 14 is, thus not inventive.
- 3.7 Claims 15 and 16 are concerned with methods for stimulating hair growth in an animal by transforming the animal with the state of the art IL-15 polynucleotide of claim 1 or treating the animal with the composition of claim 1. In view of **D1** this can not be considered inventive.
- 3.8 None of claims 17-23 seem to contain any subject-matter that, in combination with the subject-matter of any of the claims they depend on, can be considered inventive.

4. Further comments for a national/regional phase

- 4.1 For the assessment of the present claims 15 and 23 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

- 4.2 The Applicant has, in his letter of 01.09.2005, argued that **D1** merely discloses the effect of IL-15 on apoptosis and speculates on its potential use in alopecia treatment and that the application shows (page 10, lines 17-20) that "IL-15 will not merely prevent apoptosis but also stimulate and promote growth of the cells". This might be true, but the discovery of a mode of action of a known or obvious use does not make the use novel or inventive, per se.
- 4.3 For the EPO, claim 1 can not be considered as a proper "second medical use claim". Such a claim must include the disease that should be treated. "Stimulating hair growth" is not a disease but rather a mode of action, which is not allowable in a "second medical use claim". Redrafting the claim in the proper format and including the disease (e.g. alopecia) would, however, not make the claim inventive over **D1**.

amended page 3

high affinity binding to IL-15. Whereas IL-2R α is primarily expressed on activated T cells, IL-15R α mRNA has been identified in various tissues and cells. Like IL-2 the IL-15R $\alpha\beta\gamma$ complex signals through JAK1/3 and STAT3/5 pathways (3,28). IL-15 has already been described to be essential for the proliferation and maintenance of CD8⁺ memory T cells and acts, at high dose, as a pan T cell and mast cell growth factor (2,26,27). Linder, J. Invest. Dermatol., 110: 457-458 (1998) discloses that IL-15 inhibits apoptosis of keratinocytes in hair bulbs.

However, effective means for promoting hair growth and for treating, preventing and/or ameliorating the diseases referred to hereinabove are still not obtainable but nevertheless highly desirable.

Thus, the technical problem underlying the present invention must be seen as the provision of means for effectively promoting hair growth and for treating, preventing and/or ameliorating hair loss caused by or accompanied with diseases. The technical problem is solved by the embodiments characterized in the claims.

Accordingly, the present invention relates to the use of

- (i) a polynucleotide comprising
 - (a) a nucleic acid sequence as shown in SEQ ID NO: 1 or 3,
 - (b) a nucleic acid sequence encoding an amino acid sequence as shown in SEQ ID NO: 2 or 4,
 - (c) a nucleic acid sequence encoding an amino acid sequence as shown in SEQ ID NO: 2 or 4 having a modified signal peptide, a modified N-terminus and/or a modified C-terminus, or
 - (d) a nucleic acid sequence which hybridises under stringent conditions to any one of (a) to (c);
 - (ii) a polypeptide encoded by the nucleic acid as defined in any one of (a) to (d); or
 - (iii) a compound which binds to an antibody which specifically recognizes the polypeptide defined in (ii) or which specifically binds to an IL-15 receptor alpha chain
- for the preparation of a composition for stimulating hair growth.

The term "polynucleotide" relates to polynucleotides which encode a polypeptide having a biological or antigenic activity of interleukin 15 (IL-15). The structure of various IL-15 polypeptides has been described in the art and representative IL-15 polypeptides are shown in SEQ ID NO: 2 (human IL-15, Accession No. BC018149; gi34783292) and SEQ ID NO: 4

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(mouse IL-15, Accession No. BC023698; gi23271448). Several biological functions of IL-15 are also reported in the art and have been discussed herein before. An essential biological activity of IL-15 is its capability to specifically bind to the IL-15 receptor alpha chain as deposited under (Accession No. BC022705 for mouse IL-15 R α and Accession No. AY316538 for human IL-15 R α (2, Lodolce, Immunity 1998, 9: 669 – 676)). Other well characterized biological activities include its capability to stimulate NK-/NKT cells and memory T-cells (Flamand, J. Clin. Invest, 1996, 97: 1373 - 81; Kv, Science 2000, 288: 675 - 678) and its proliferative effect on lymphoid or mesenchymal cells as well as the prevention of apoptosis after induction with apoptic substances (14). Preferably, said biological activity is the stimulation of hair growth and keratinocytes as demonstrated in the accompanied Examples. An essential antigenic activity is its capability to be specifically recognized by a specific, i.e. non-cross-reactive, IL-15 antibody as disclosed in Shinozaki, J. Clin. Invest, 2002, 109: 951 – 960. Such an IL-15 antibody can also be obtained by routine methods. Preferably, the antibody is a monoclonal antibody. These activities can be tested by routine methods well known in the art and described in the above cited references in detail. Most preferably, the polynucleotides of the present invention have a nucleic acid sequence as shown in SEQ ID NO: 1 (human IL-15) or SEQ ID NO: 3 (mouse IL-15).

Preferably, the IL-15 polynucleotides also encompass variant polynucleotides which are capable to hybridise with the polynucleotides shown in SEQ ID NO: 1 or SEQ ID NO: 3 under stringent hybridisation conditions. More preferably, said conditions are disclosed in Ausubel, 2001, Current protocols in molecular biology. Said polynucleotides are most preferably at least 70 %, at least 80 %, at least 85 %, at least 90 %, at least 95 %, at least 96 %, at least 97 %, at least 98 % or at least 99 % identical with SEQ ID NO: 1 or SEQ ID NO: 3.

The variant polynucleotides of the invention may comprise a modified signal peptide or leader sequence, i.e. amino acids 1 to 48 of SEQ ID NO: 2, amino acids 1 to 48 of SEQ ID NO: 4 and amino acids corresponding thereto in polypeptide variants thereof. Modifications meant hereby are those which increase the secretion of IL-15 from a cell. Biological assays for testing whether a modification increases said secretion are well known in the art and are described in (5) and (6). Most preferably, the signal peptide is modified by replacing it with the signal peptide of CD33 polypeptide (Accession No. NM 02 1293). Moreover, the N- or C-terminal amino acids of the mature polypeptide shown in SEQ ID NO: 2 or SEQ ID NO: 4 or amino acids corresponding thereto in the polypeptide variants may be modified as to increase stability of the mature polypeptides. The stability of mature IL-15 polypeptides can be tested

Amended set of claims

1. Use of

- (i) a polynucleotide comprising
 - (a) a nucleic acid sequence as shown in SEQ ID NO: 1 or 3,
 - (b) a nucleic acid sequence encoding an amino acid sequence as shown in SEQ ID NO: 2 or 4,
 - (c) a nucleic acid sequence encoding an amino acid sequence as shown in SEQ ID NO: 2 or 4 having a modified signal peptide, a modified N-terminus and/or a modified C-terminus, or
 - (d) a nucleic acid sequence which hybridises under stringent conditions to any one of (a) to (c);
- (ii) a polypeptide encoded by the nucleic acid as defined in any one of (a) to (c); or
- (iii) a compound which binds to an antibody which specifically recognizes the polypeptide defined in (ii) or which specifically binds to an IL-15 receptor alpha chain

for the preparation of a composition for stimulating hair growth.

- 2. Use of a polynucleotide, polypeptide or compound as defined in claim 1 for the preparation of a composition for treating, preventing and/or ameliorating hair loss.
- 3. The use of claim 1 or 2, wherein said composition further comprises a second hair growth stimulating agent.
- 4. The use of claim 3, wherein said second hair growth stimulating agent is selected from the group consisting of zinc salts of carboxylic acids, saponins, triterpenes, preferably oleanolic acid or ursolic acid, crataegolic acid, celastrol, Asiatic acid, inhibitors of 5-[alpha]-reductase, preferably progesterone, 1,4-methyl-4-azasteroids, preferably 17-[beta]-N,N-diethylcarbamoyl-4-methyl-4-aza-5-[alpha]-androstan-3-one, androgen receptor antagonists, preferably cyproterone acetate, Minoxidil(R), azaelaic acid and derivatives thereof, cyclosporin, triiodothyronine, diazoxide, potassium channel openers, preferably cromakalin, phenytoin, and mixtures thereof, and derivatives of oestrogen, preferably oestradiolvalerate.

5. The use of any one of claims 1 to 4, wherein said composition further comprises a pharmaceutically or cosmetically acceptable carrier.
6. The use of any one of claims 1 to 5, wherein said composition is a pharmaceutical composition.
7. The use of any one of claims 1 to 5, wherein said composition is a cosmetic composition.
8. The use of any one of claims 1 to 7, wherein said composition is formulated as a hair tonic, a hair restorer composition, a shampoo, a powder, a jelly, a hair rinse, an ointment, a hair lotion, a paste, a hair cream, a hair spray and/or a hair aerosol.
9. The use of any one of claims 1 to 8, wherein said composition is to be administered topically to the skin or scalp of a subject.
10. The use of claim 9, wherein said subject is a mammal.
11. The use of claim 10, wherein said mammal is a human, a dog, a cat, a horse, a rabbit, a sheep, a camel, a mouse, a rat, an alpaca, a vicuna, a guanaco or a lama.
12. The use of any one of claims 9 to 11, wherein said subject suffers from genetically determined and/or acquired form of hair loss.
13. The use of claim 12, wherein said genetically determined or acquired form of hair loss is alopecia areata, alopecia subtotalis, alopecia totalis, trichotillomania or drug induced alopecia.
14. A transgenic non-human animal comprising a nucleic acid as defined in claim 1, wherein said nucleic acid is specifically expressed in the keratinocytes of the hair bulb, in the Langerhans cells, in the melanocytes, in the dendritic epidermal T-cells, in the mast cells, in cutaneous nerve fibres or in fibroblasts.
15. A method for stimulating hair growth in a non-human animal comprising the steps of:

- (a) Transforming said animal with a nucleic acid as defined in claim 1; and
 - (b) Expressing the polypeptide encoded by said nucleic acid.
16. A method for manufacturing non-human animal hair comprising the steps of:
- (a) Transforming said non-human animal with a nucleic acid as defined in claim 1; and
 - (b) Expressing the polypeptide encoded by said nucleic acid.
17. The method of claim 15 or 16, wherein said IL-15 polypeptide is expressed under the control of a regulatory element.
18. The method of claim 17, wherein said regulatory element enables specific expression in the keratinocytes of the hair bulb, in the Langerhans cells, in the melanocytes, in the dendritic epidermal T-cells, in the mast cells, in cutaneous nerve fibres or in fibroblasts.
19. The method of any one of claims 16 to 18, further comprising the step of administering to the skin and/or scalp of a non-human animal the composition as defined in claim 1.
20. A method for manufacturing non-human animal hair comprising the step of administering to the skin and/or scalp of a non-human animal the composition as defined in claim 1.
21. The method of any one of claims 16 to 20, further comprising the step of obtaining the hair of said non-human animal.
22. The transgenic non-human animal of claim 14 or the method of any one of claims 15 to 21, wherein said animal is a dog, a cat, a horse, a rabbit, a sheep, a camel, a mouse, a rat, an alpaca, a vicuna, a guanaco or a lama.
23. A method of treating, preventing and/or ameliorating a subject which suffers from hair loss comprising the step of administering a composition as defined in claim 1 in an effective dosage to said subject.

Figure 5

mIL-15 mRNA - modified Sequence

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1  cttctgtcca gccactcttc cccagagttc tcttcttcat cctccccctt gcagagtagg
61  gcagcttgca ggtcctcctg caagtctctc ccaattctct gcgccccaaa gacttgcagt
121 gcatctcctt acgcgctgca gggaccttgc cagggcagga ctgcccccg cagttgcag
181 agttggacga agacgggatc ctgctgtgtt tggaaggctg agttccacat ctaacagctc
241 agagaggtca ggaaagaatc caccttgaca catggccctc tggctcttca aagcactgcc
301 tcttcatggt ccttgctggt gaggtcctta agaacacaga aacctatgtc agcagataac
361 cagcctacag gaggccaaag agagttctgg atggatggca gctggaagcc catcgccata
421 gccagctcat cttcaacatt gaagctctta cctgggcatt aagtaatgaa aattttgaaa
481 ccatatatga ggaatacatc catctcgtgc tacttgtgtt tccttctaaa cagtcacttt
541 ttaactgagg ctggcattca tgtcttcatt ttgggctgtg tcagtgtagg tctccctaaa
601 acagaggcca actggataga tgtaagatat gacctggaga aaattgaaag ccttattcaa
661 tctattcata ttgacaccac tttatacact gacagtgact ttcattcccag ttgcaaagtt
721 actgcaatga actgctttct cctggaattg caggttattt tacatgagta cagtaacatg
781 actcttaatg aaacagtaag aaacgtgctc taccttgcaa acagcactct gtcttctaac
841 aagaatgtag cagaatctgg ctgcaaggaa tgtgaggagc tggaggagaa aaccttcaca
901 gagtttttgc aaagctttat acgcattgtc caaatgttca tcaacacgtc ctgactgcat
961 gcgagcctct tccgtgtttc tgttattaag gtacctccac ctgctgctca gaggcagcac
1021 agctccatgc atttgaaatc tgctgggcaa actaagcttc ctaacaagga gataatgagc
1081 cacttgatc acatgaaatc ttggaaatga agagaggaaa agagctcgtc tcagacttat
1141 ttttgcttgc ttatttttaa tttattgctt catttgtaca tatttgtaat ataacagaag
1201 atgtggaata aagttgtatg gatattttat caattgaaat ttaaaaaaaaa
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